Incidentally Detected Giant Oncocytoma Arising in Retroperitoneal Heterotopic Adrenal Tissue

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• A nonfunctional retroperitoneal oncocytoma incidentally discovered in a 40-year-old woman is described. The tumor, which was 17 cm in largest dimension, was completely separated from the kidneys and adrenal glands and consisted of nests of polygonal cells with large, granular, eosinophilic cytoplasm. Significant nuclear atypia, necrosis, and mitosis were absent. Ultrastructural analysis confirmed the oncocytic nature of the neoplastic cells. Since neoplastic cells were not immunoreactive for chromogranin and did not contain dense-core secretory granules, the diagnosis of oncocytic paraganglioma was excluded. Cells immunoreactive for 3β-hydroxysteroid dehydrogenase, the enzyme catalyzing the conversions of pregnenolone to progesterone and dehydroepiandrosterone to androstenedione, were identified in the tumor, thus strongly indicating adrenocortical tissue origin. Multiple nests of 3β-hydroxysteroid dehydrogenase–positive cells were detected in the loose retroperitoneal connective tissue. These findings strongly support the origin of the tumor from heterotopic retroperitoneal rests of the adrenal gland. To our knowledge, only 1 similar case has been described in the literature to date.

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The term *oncocytoma* is used to indicate a tumor composed of cells with large granular cytoplasm packed with mitochondria arranged in alveolar, tubular, or solid patterns.[1] Oncocytic features have been observed in tumors arising in salivary glands, thyroid, kidney, adrenal gland, adenohypophysis, lung, liver, breast, bladder, ovary, stomach, small intestine, paraganglia, thymus, prostate, and soft tissues, as well as in plasmocytoma.[1]

When located in the retroperitoneum, pure oncocytic tumors are either renal or adrenal in origin.[1–4] Adrenal oncocytomas are mostly adrenocortical in origin, whereas oncocytic pheochromocytomas are admittedly extremely rare.[5] In 1 case of retroperitoneal oncocytoma, the origin from heterotopic adrenocortical tissue was suggested for a tumor completely separated from the kidneys and adrenal glands.[6]

In this article, we describe the clinicopathologic features of a giant, incidentally discovered, retroperitoneal oncocytoma without any continuity with either the ipsilateral kidney or the orthotopic adrenal gland. The adrenocortical nature of the tumor was proven by immunoreactivity for 3β-hydroxysteroid dehydrogenase (3β-HSD), the enzyme catalyzing the conversion of pregnenolone to progesterone and dehydroepiandrosterone to androstenedione. Scattered nests of 3β-HSD–positive cells were identified in the retroperitoneal adipose tissue well outside the tumor capsule. Together with the physical separation of the tumor from the adrenal gland, these findings strongly suggest the origin of the tumor from heterotopic retroperitoneal adrenal rests.

REPORT OF A CASE

A 40-year-old woman with gastroesophageal reflux was seen as an outpatient for routine follow-up. Her past medical history was not otherwise significant. On physical examination, she was normotensive and showed no evidence of virilization or a cushingoid habitus. Endoscopy revealed compression of the gastric wall. Based on this feature, abdominal computed tomography (Figure 1, a) and angiography (Figure 1, b and c) were performed. The computed tomographic scan demonstrated a 17 × 15-cm mass in the left retroperitoneal space with ptosis of the ipsilateral kidney. No other masses were detected in adjacent lymph nodes or distant organs. Because of the location and the angiographic finding of a significantly enlarged inferior suprarenal artery, the mass was interpreted as a primitive tumor of the adrenal gland. For this reason, serum and urine endocrinological testing was performed, including evaluations for catecholamines and their metabolites, but these tests failed to reveal any abnormality. At surgery, there was no cardiovascular instability with the administration of anesthesia, and the mass was found to be completely separated from the kidney and adrenal gland; resection en bloc of the mass with the grossly normal adjacent adrenal gland was performed. The patient's postoperative recovery was unremarkable. She received no further treatment and was alive and free of disease 8 months after surgery.

MATERIALS AND METHODS

After fixation with 4% formalin, multiple specimens of the tumor were routinely processed for paraffin embedding. Five-micrometer-thick sections were stained with hematoxylin-eosin, Gomori reticulin, and phosphotungstic acid–hematoxylin solution.

Immunohistochemical analysis was performed by means of the peroxidase-antiperoxidase method. The primary antibodies used

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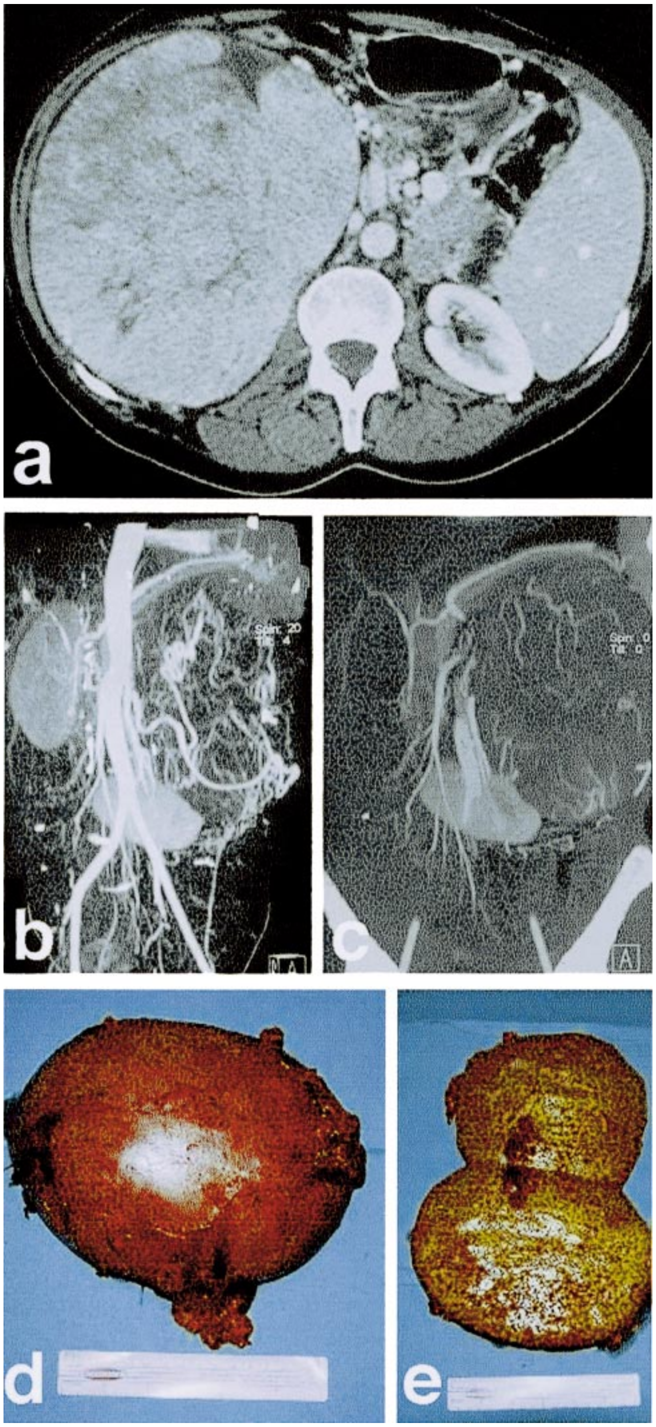

Figure 1. *Tomographic (a) and angiographic (b, c) views of the mass. Note that the tumor is mainly vascularized by the inferior suprarenal artery. Gross pathology (d) reveals a solid tumor with smooth external surface. The cut surface (e) is homogeneously tan-brown.*

in this study are listed in the Table. Age-matched adrenocortical tissue was used as positive control for sections treated with the polyclonal antibody generated against 3β-HSD. Sections to be immunostained for cytokeratins, vimentin, neuron-specific enolase, epithelial membrane antigen, chromogranin A, and Ki-67 were treated in a microwave oven 3 times for 5 minutes in 0.01M sodium citrate buffer, pH 6. The color reaction was developed using 3,3′-diaminobenzidine tetrahydrochloride (DAB, Sigma, St Louis, Mo) as the substrate. Using the MIB-1 antibody, the tumor proliferative fraction was determined as the number of immunolabeled nuclei per 1000 cells counted, as previously reported.[7]

For transmission electron microscopy, small samples of the tumor were routinely processed for epoxy resin (Araldite) embedding and thin sectioning. Semithin sections were stained with azure II–methylene blue to select appropriate fields. Ultrathin sections were contrasted with uranyl acetate and lead citrate and examined with a CM 10 Philips electron microscope.

RESULTS

Gross examination showed a solid encapsulated tumor sharply separated from the adjacent adrenal gland (Figure 1, d and e). The tumor weighed 1800 g and measured 17 cm in largest dimension. The cut surface was tan-brown and partially lobulated by fibrous septa and did not show necrosis or cystic changes. Loose connective tissue separated the tumor from the adjacent adrenal gland, which was grossly unremarkable.

Histologic examination did not reveal abnormalities in the adrenal gland. The tumor was surrounded by a thick fibrous capsule and was composed exclusively of cells with abundant, eosinophilic, granular cytoplasm (Figure 2, a). The neoplastic cells were arranged in nests (better evident after silver staining), which were separated by an abundant capillary network. Cellular atypia, mitosis, necrosis, and capsular and/or vascular invasion were absent. Phosphotungstic acid–hematoxylin staining was uniformly positive, although variable from cell to cell (Figure 2, b). Small aggregates of lymphocytes, plasma cells, and histiocytes were dispersed within the tumor. Transmission electron microscopy confirmed the oncocytic nature of the neoplastic cells by establishing that their light microscopic appearance was the result of the abnormal accumulation of mitochondria. Dense-core, membrane-bound cytoplasmic granules were not detected.

Immunohistochemical results are summarized in the Table. The neoplastic cells were immunoreactive for cytokeratins 8 and 18 and for vimentin. Results of immunostaining for epithelial membrane antigen, neuron-specific enolase, S100 protein, and chromogranin A were negative. Compared to healthy age-matched adrenocortical tissue (Figure 3, d), in which immunoreactivity for 3β-HSD was diffusely detected, sparse groups of neoplastic cells (<10%) were immunolabeled in the tumor (Figure 3, a and b). Cells immunoreactive for 3β-HSD were also detected in retroperitoneal connective tissue outside the boundary of the orthotopic adrenal gland and were interpreted as accessory adrenal cortical tissue (Figure 3, e through h). Using the MIB-1 antibody, the tumor proliferative fraction was 28.

COMMENT

The tumor described here fulfilled all morphologic diagnostic criteria for an oncocytic neoplasm.[1] When located in the retroperitoneum, oncocytic tumors have been reported as renal or adrenal in origin. In the adrenal gland, they have been classified as either oncocytic adenoma, carcinoma, tumors of undetermined malignant potential,[1–4] or pheochromocytoma.[5] Although the alveolar pattern could be consistent with an oncocytic (extra-adrenal) paraganglioma, this diagnosis was excluded by the absence of abnormalities in plasma and urine catecholamines and their metabolites, lack of immunoreactivity for chromogranin A, and absence of dense-core, membrane-bound granules by transmission electron microscopy.

The tumor was completely separated from both kidney

Primary Antibodies Used in This Study and Immunoreactivity of the Neoplastic Cells*				
Antibody	**Source**	**Dilution**	**Pretreatment**	**Reaction**
CK (MNF116)	Dako Corporation, Carpinteria, Calif	1:50	M	+
CK-8 (35βH11)	Dako	1:25	M	+
CK-18 (DC10)	Dako	1:25	M	+
Vim (V9)	Dako	1:50	M	+
NSE (H14)	Dako	1:50	M	−
EMA (E29)	Dako	1:25	M	−
CGR (Dak-A3)	Dako	1:30	M	−
S100	Dako	1:400	None	−
3β-HSD	J. L. Thomas†	1:200	None	+
Ki-67 (MIB-1)	DBA ITALIA, Segrate, Italy	1:100	M	TPF: 28

* CK indicates cytokeratin; Vim, vimentin; NSE, neuron-specific enolase; EMA, epithelial membrane antigen; CGR, chromogranin; 3β-HSD, 3β-hydroxysteroid dehydrogenase; M, microwave oven; and TPF, tumor proliferative fraction (number of positive cells/1000 cells).

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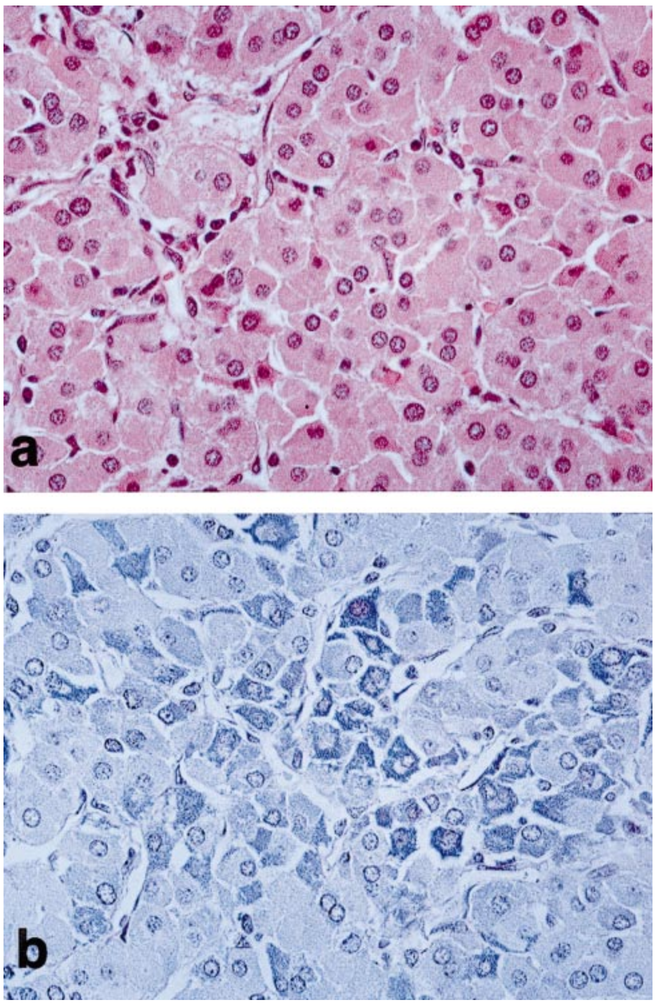

Figure 2. *Light microscopy. a, The tumor is composed of nests of cells with abundant, eosinophilic, granular cytoplasm without atypia (hematoxylin-eosin, original magnification ×240). b, Phosphotungstic acid–hematoxylin staining was uniformly positive, although variable from cell to cell (original magnification ×240).*

and the orthotopic adrenal gland. However, an adrenocortical origin of the tumor was strongly supported by the expression of the key steroidogenic enzyme 3β-HSD in a proportion (<10%) of tumor cells. For this reason, heterotopic adrenocortical tissue appeared to be a plausible site of origin for this tumor. 3β-Hydroxysteroid immunostaining also highlighted multiple small nests of immunoreactive cells residing in the loose retroperitoneal connective tissue, at variable distance from the orthotopic adrenal gland. This is the single most common site for heterotopic rests of adrenocortical tissue. Thus, evidence of actual adrenal rests in the region where the tumor developed was indeed present in our case. This view seems to be strongly supported by the demonstration of 3β-HSD–immunoreactive cells in the connective tissue surrounding the orthotopic adrenal gland and by the presence of sparse groups of neoplastic cells immunolabeled by the same antibody. 3β-Hydroxysteroid is expressed in diverse fetal and adult human tissues involved in steroid metabolism, including gonads, adrenal glands, placenta, prostate, and breast.[8–10] In the adrenal gland, this enzyme is immunodetectable in all 3 zones of the cortex from 7 months to 8 years, thereafter decreasing in the zona reticularis.[8] To date, only 1 other case of oncocytoma arising from retroperitoneal heterotopic adrenocortical tissue has been described in the literature.[6] In that case, the origin from heterotopic adrenocortical tissue was suggested by the presence of scattered tumor cells showing abundant smooth endoplasmic reticulum. In our case, the expression of 3β-HSD provides additional evidence for the origin of the tumor from steroidogenic tissue. Although the enzyme is also expressed in the gonads, retroperitoneal rests of steroidogenic tissue are usually considered to be adrenal rests. Hence, adrenal rests appear to be a plausible site of origin for the tumor in the present case.

Most oncocytic tumors arising in endocrine organs are nonfunctional.[5] Among the adrenocortical oncocytomas described in the literature, only 1 was associated with an endocrine syndrome (virilization).[2] Expression of 3β-HSD was restricted in our case to a minority of tumor cells, suggesting that only a minority of cells would be active in steroidogenesis, thus making the tumor hormonally inexpressive. A similar inference was made earlier for 3 orthotopic adrenocortical oncocytomas tested by immunohistochemistry for different steroidogenic enzymes, including 3β-HSD.[3] In 2 of these tumors, scattered weak positivity was detected only for P-450scc (cholesterol side-chain cleavage), the enzyme that catalyzes the conversion of cholesterol to pregnenolone.

Many features suggest that the tumor reported here is benign. First, oncocytomas are usually benign tumors[1]; second, no recurrence or metastasis was observed within

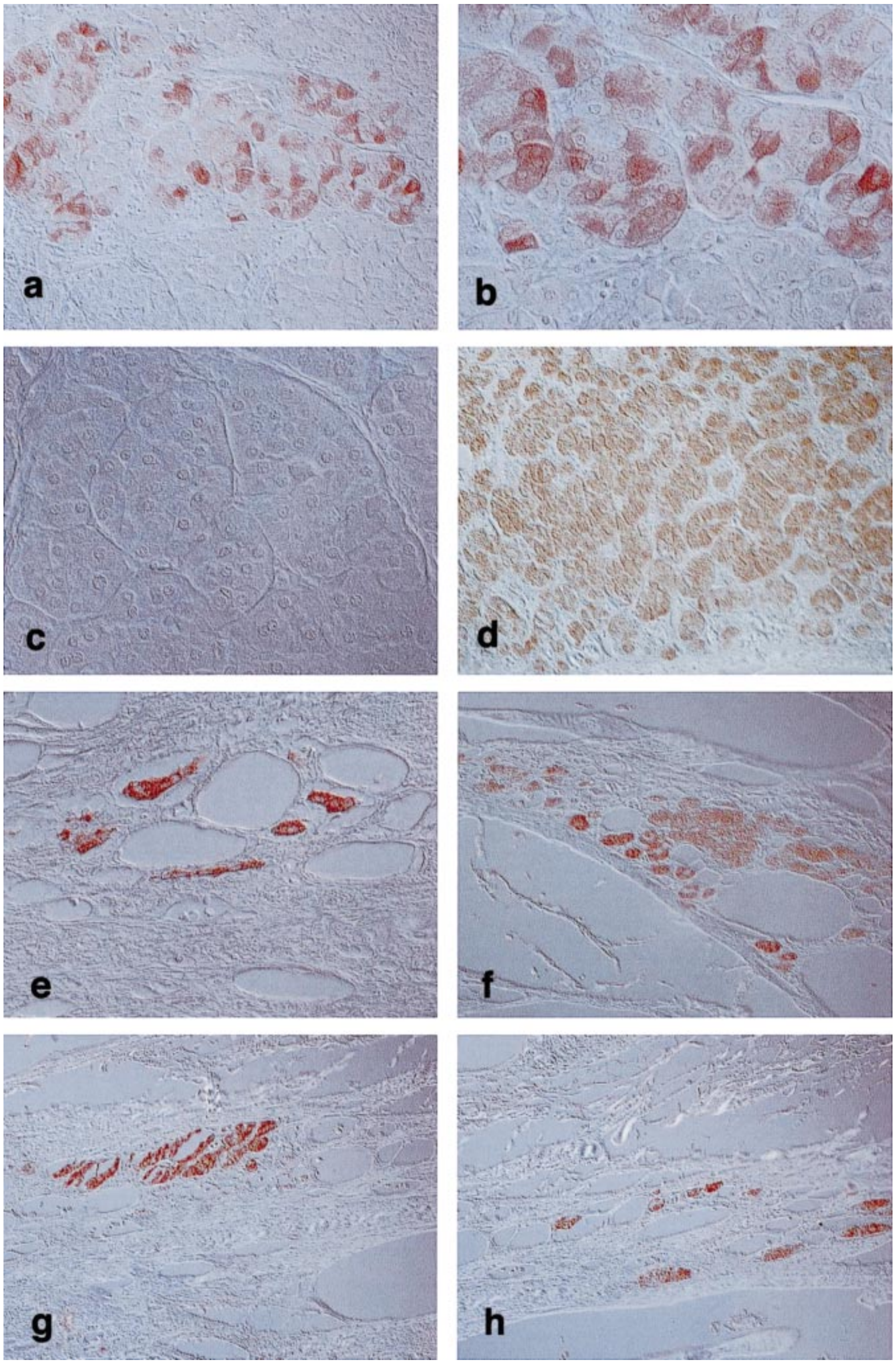

Figure 3. *3β-Hydroxysteroid dehydrogenase (3β-HSD) immunohistology. a and b, A cluster of 3β-HSD–expressing cells within the tumor (original magnifications ×160 [a] and ×220 [b]). c, Negative control (original magnification ×220). d, Healthy adrenocortical gland, positive control (original magnification ×160). e through h, Multiple nests of 3β-HSD–positive cells are scattered in the loose fibroadipose tissue outside the orthotopic adrenal gland (DAB reaction, Nomarski optics, original magnifications ×120).*

the 8 months following surgery. In addition, the benign nature of this tumor is supported by the criteria proposed by Weiss et al[11,12] and Vargas et al[7] to discriminate adrenocortical adenoma and carcinoma. Weiss et al[11,12] demonstrated that when 3 or more histologic findings among high-nuclear-grade atypia, eosinophilic cell cytoplasm (>75%), diffuse architecture (>33%), necrosis, typical (>5 mitoses/50 high-power fields) and atypical mitotic figures, and capsular, vascular, and sinusoidal invasion are present, the diagnosis of malignancy is adequate. Of these histologic criteria, only eosinophilic cytoplasm was present in more than 75% of the neoplastic cells in our case. However, this criterion is of doubtful significance as applied to an oncocytoma, which by definition (at variance with a nononcocytic adrenocortical tumor) is composed of deeply eosinophilic cells. Although the weight of an adrenocortical neoplasm shows only marginal statistical association with poor prognosis and is not entirely predictive of biological behavior by itself,[11,12] the impressive size of this tumor cannot go unnoticed. However, the significance of tumor size as a prognostic indicator is perhaps even more questionable as applied to oncocytomas. In the kidney, for example, it is not uncommon for fully benign oncocytic tumors to grow to significant size before being incidentally discovered. Perhaps more stringent criteria can be derived by assessing the proliferation potential within these tumors. Using the MIB-1 antibody on 40 adrenocortical lesions (10 cases of hyperplasia, 10 adenomas, 12 carcinomas, and 8 metastatic and recurrent carcinomas), Vargas et al[7] demonstrated that none of the benign lesions had a tumor proliferative fraction greater than 80; in our case, the tumor proliferative fraction was 28. Longer follow-up in our case and analysis of more cases will provide additional clues to the general biological behavior of orthotopic and heterotopic adrenocortical oncocytomas.

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